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Statistical Review for PMA P030004, Onyx LES Liquid Embolic System, Micro Therapeutics, Inc.

## I. Introduction

The Micro Therapeutics Onyx Liquid Embolic System is a liquid embolic device. The device is intended for use by Interventional Neuro-Radiologist when therapeutic or palliative embolization of a brain arteriovenous malformation (BAVM) is indicated to minimize blood loss or to reduce the BAVM size prior to surgery.

The liquid Onyx is a mixture of ethylene vinyl alcohol copolymer dissolved in dimethyl sulfoxide (DMSO). Micronized tantalum powder is suspended in the liquid polymer/DMSO mixture to provide fluoroscopic visualization. The Onyx material is delivered in a liquid phase through a micro catheter to the target lesion under fluoroscopic control. Upon contact with blood the solvent rapidly diffuses away causing in-situ precipitation of a soft radiopaque polymeric embolus.

This PMA included results from a randomized controlled trial comparing the experimental Onyx device to the marketed Butyl Cyano-Acrylate (BCA) device to demonstrate the equivalence of the devices in safety and effectiveness.

## II. Sponsor's Results and Reviewer's Comments

1. According to Figure 3.1 Patient flowchart (page 3139), the study randomized a total of 108 patients (57 in the control n-BCA group and 51 in the experimental Onyx group), of which 54 n-BCA patients and 46 Onyx patients were treated. As shown in Table 1 (page 3135), stated on page 3135 and concluded on page 3137, sponsor's **intent-to-treat** results that the experimental Onyx was statistically superior to the control n-BCA device in technical success proportion when measured by angiographic reduction in AVM size of 50% or greater, was based on **51** n-BCA patients and **42** Onyx patients, not based on all **108** randomized patients (57 n-BCA patients

and 51 Onyx patients).

For the intent-to-treat analysis, all randomized patients needed to be included to preserve the random allocation of the treatments.

2. The per protocol result as shown in Table 1 (page 3135) was based on 49 control patients and 43 experimental patients, sponsor's result based on data pooled over 20 centers indicated the experimental device was not inferior to the control device. However, as noted in 3 and 4 below, the effects of center and co-variables on the treatment need to be further investigated.

3. The study included a total of twenty (20) study centers; it is not clear if the treatment effect differed among study centers. Note that data cannot just be pooled and center effect be ignored. Statistical model, such as meta analysis, including center and treatment by center interaction effects needs to be used in data analysis

Sponsor's justification of pooling data over 20 centers (page 3149) by comparing baseline variables among sites is not adequate, since number of patients per center is very small and the statistical tests used only have limited power. Further note that, regardless of small sample size, a statistically significant difference was detected in AVM size among sites.

4. Based on all 108 randomized patients (Exhibit 11) and also 102 of the 108 randomized patients, baseline co-variables were compared between the treatment groups. Differences between the treatment groups were noted, for example, in proportion of patients who had aneurysms. Both for the intent-to-treat analysis and the per protocol analysis, in addition to the above mentioned center and treatment by center interaction effects, the treatment effect needs to be adjusted for the co-variables. Logistic regression analysis is recommended.

5. Based on 100 treated patients, the number of injections required was shown (Table 14, page 3150). No statistically significant treatment difference was found. The mean number of injections per patient was 2.5 injections in both treatment groups.

Adjunctive procedures were performed more frequently in the control n-BCA group (Table 16, page 3152). The difference was statistically significant.

6. No statistically significant treatment difference was found between the treatment groups in neurological outcomes, such as NIH stroke score (Table 18, page 3157), Barthel Index (Table 19, page 3157) and Glasgow outcome scale (Table 20, page 3158). Further, no statistically significant difference was found in blood loss and in surgical resection time. However, both blood loss and resection time had large variances; the lack of statistically significant result cannot be taken as device equivalence in these variables.

7. For the 100 treated patients (54 in the control n-BCA group and 46 in the Onyx group), serious adverse events, were shown (Table 28, page 3175). Nineteen patents treated with Onyx and 15 patients treated with n-BCA had serious adverse events, such as death, intracranial hemorrhage, stroke, worsening neurological status, hydrocephalus, seizures or headache, nausea and vomiting. The sponsor indicated that the difference is not statistically significant (p-value=0.2). However, note that the serious adverse event rate is numerically higher in the experimental group. If not counting the two cases of headache, nausea and vomiting in the n-BCA group as serious, the rates are 24.1% and 41.3% in n-BCA and Onyx groups, respectively, with a difference of 17.2%. The 2-sided 95% confidence interval is (-0.02, 0.35). The treatment difference needs to be clinically evaluated.

8. Among the 100 treated patients, the frequencies of technical/procedural events were compared (page 3153). The frequencies of technical events occurred more frequently in the Onyx group 18/46 as compared to that in the n-BCA group 11/54. The n-BCA control patients experienced more procedural events (12/54) than the Onyx patients (3/46).

In conclusion, Sponsor’s results from the above clinical study did not unequivocally demonstrate the safety and effectiveness of the experimental device. The sponsor needs to respond to the above comments 1-4 and 7.

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